

## CLAIMS

1. A screening method for better ascertaining at least one variable selected from the group consisting of (1) the likelihood of the presence of a tumor in a subject suspected of having a tumor, (2) the likelihood of the presence of a malignant tumor in a subject suspected of having a malignant tumor (3) the likelihood of the presence of a tumor metastasis in a subject suspected of having a tumor metastasis, and (4) the likely progression of a malignant tumor in a subject, the method comprising

(a) determining the level of a marker, selected from the group consisting of (i) PAI-1 protein abundance, (ii) uPA:PAI complex abundance (iii) the change in PAI-1 protein abundance over time, and (iv) the change in uPA:PAI complex abundance over time, in a test sample, and, in the case of (iii) and (iv) above, over a plurality of test samples taken at different times,

said test sample or samples being of or derived from a body fluid or tissue of said subject,

said tumor being of a kind such that there is a correlation between the level of said marker and at least one of variables (1)-(4) above, and

(b) correlating the level of said marker for said sample or samples, and the reference level of said marker for a corresponding reference sample or samples,

whereby at least one of variables (1)-(4) is better ascertained.

2. The method of claim 1 where the variable (1) is ascertained.

3. The method of claim 1 where the variable (2) is ascertained.

4. The method of claim 1 where the variable (3) is ascertained.

5. The method of claim 1 where the variable (4) is ascertained.

6. The method of claim 1 where the marker is (i).

7. The method of claim 1 where the marker is (ii).
8. The method of claim 1 where the marker is (iii).
9. The method of claim 1 where the marker is (iv).
10. The method of claim 1 where the tumor is a breast  
5 tumor.
11. The method of claim 1 where the tumor is a gastric  
tumor.
12. The method of claim 1 where the tumor is a colon  
tumor.
- 10 13. The method of claim 1 where the tumor is a lung  
tumor.
14. The method of claim 1 where the tumor is an  
ovarian tumor.
15. The method of claim 14 where the marker is (i) and  
the variable is (1).
16. The method of claim 1 where the marker is (i), the  
variable is (4), and the tumor is selected from the group  
consisting of breast, gastric, colon, and lung cancers.
17. The method of claim 1 in which the sample is a  
frozen, unfixed tumor tissue sample or extract thereof.
18. The method of claim 17 where the marker is (i) and  
(4) is better ascertained.
19. The method of claim 18 where the tumor is selected  
from the group consisting of breast, gastric, colon, lung,  
25 and ovarian cancer.
20. The method of claim 1 in which the sample is a  
body fluid.
21. The method of claim 17 in which the sample is  
plasma.
- 30 22. The method of claim 21 in which the marker is (i)  
and the tumor is a pancreatic, ovarian, urinary tract,  
colon, colorectal or breast tumor.
23. The method of claim 21 in which the marker is  
(iii), and (4) is ascertained.
- 35 24. The method of claim 23 in which a first sample is  
taken preoperatively and a later sample is taken post

operatively.

25. The method of claim 24 in which the tumor is a colon tumor.

26. The method of claim 7 in which the tumor is a breast tumor, and the sample is a cytosol.

27. The method of claim 1 in which (3) applies, and the method determines whether there is more than a 40% risk of tumor metastasis within about five years.

28. The method of claim 1 in which (4) applies, and the method determines whether the subject has at least a 50% higher risk of death.

29. The method of claim 1 where said level is determined by an immunoassay.

30. The method of claim 29 where said level is determined by a binding assay in which one of the assay reagents is a monoclonal antibody which binds a human endothelial type plasminogen activator inhibitor produced by dexamethasone-treated human HT-1080 fibrosarcoma cells (ATCC CCL121).

31. The method of claim 30 where said marker is (iii) or (iv) and said antibody further binds to a complex comprising urokinase-type plasminogen activator and ePAI.

32. The method of claim 30 where said antibody binds specifically to an antigenic determinant of human ePAI which is also specifically bound by the monoclonal antibody secreted by the hybridoma of clone 2.

33. The method of claim 31 where said antibody binds specifically to an antigenic determinant of human ePAI which is also specifically bound by the monoclonal antibody secreted by the hybridoma of clone 4.

34. The method of claim 1 where the malignant tumor is selected from the group consisting of mammary carcinomas, urological carcinomas, gynecological carcinomas, non-small cell lung tumors, gastrointestinal cancers, brain tumors, sarcomas, haematological malignancy and skin cancers.

35. The method of claim 1 which further comprises

monitoring the progression of the tumor in a patient by determining the level of the marker at a plurality of different times and correlating said levels with the times of determination.

5           36. A method of detecting the presence or predicting the progression of a malignant tumor in a subject having or suspected of having a malignant tumor, the method comprising

10           (a) determining at a first point in time (I) one or more of PAI-1 DNA abundance, PAI-1 mRNA abundance, or PAI-1 protein abundance in tumor tissue or a sample of a body fluid such as plasma, serum or urine from said subject,

          (b) determining at a later point in time (II) one or more of PAI-1 DNA abundance, PAI-1 mRNA abundance, or PAI-1 protein abundance in a sample of body fluid from said subject,

          (c) determining the difference between the abundance of said PAI-1 DNA, PAI-1 mRNA, or PAI-1 protein determined at said first point in time (I) with the value determined at said later point in time (II), and

          (d) correlating said difference with an established level of difference which is indicative of a high likelihood of tumor presence or metastasis.

25           37. A method according to claim 36 wherein said first point in time (I) is preoperatively.

          38. A method according to claim 36 wherein said second point in time (II) is at least 2 weeks postoperatively.

30           39. A method according to claim 36, wherein the malignant tumor is selected from the group consisting of mammary carcinomas, urological carcinomas, gynaecological carcinomas, non-small cell lung tumors, gastrointestinal cancers, brain tumors, sarcomas, haematological malignancy and skin cancers.

35           40. A method of predicting the presence or progression of a malignant tumor in a subject having or suspected of

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having a malignant tumor, the method comprising

- (a) determining at a first point in time (I) uPA:PAI-1 complexes in a sample of a tissue or a body fluid from said subject,
- 5 (b) determining at a later point in time (II) uPA:PAI-1 complexes in a sample of a tissue or body fluid from said subject,
- (c) determining the difference between the abundance of said uPA:PAI-1 complexes determined at said first point in time (I) with the abundance  
10 determined at said later point in time (II), and
- (d) correlating said difference with an established level of difference which is indicative of high likelihood of tumor presence or metastasis.

41. A method according to claim 40 comprising the steps of:

- (a) testing a tissue section from a malignant tumor or a sample of a body fluid from a patient having or suspected of having a malignant tumor, said sample taken at a first point in time (I), with an antibody reagent specific for uPA:PAI-1 complexes under antibody binding conditions,
- (b) determining the binding of the reagent to uPA:PAI-1 complexes in said tissue section or  
25 sample of a body fluid taken at said first point in time (I),
- (c) testing a sample of a tissue or a body fluid from a patient having or suspected of having a malignant tumor, said sample taken at a later  
30 point in time (II), with an antibody reagent specific for uPA:PAI-1 complexes under antibody binding conditions,
- (d) determining the binding of the reagent to uPA:PAI-1 complexes in said sample taken at said later  
35 point in time (II),
- (e) determining the difference between the level of

said uPA:PAI-1 complexes determined at said first point in time (I) with the value determined at said later point in time (II), and

- (f) correlating said difference with an established level of difference which is indicative of a high likelihood of tumor presence or metastasis.

42. A method according to claim 40, wherein the determination of the uPA:PAI-1 complexes is performed by using an immuno-assay, such as an ELISA or RIA, or by using an activity assay.

43. A method of predicting the prognosis of an individual subject having or suspected of having a malignant tumor, the method comprising

- (a) determining the level of uPA:PAI-1 complexes in malignant or potentially malignant tissue or body fluid from a number of subjects having a malignant tumor,
- (b) establishing a threshold level of uPA:PAI-1 complexes above or equal to which a value is indicative of a high likelihood of non-clinically evident tumor metastasis resulting in a poor prognosis,
- (c) correlating the level of uPA:PAI-1 complexes of the individual subject with the value established in (b) in order to determine the prognosis of the individual subject, and optionally
- (d) if the likelihood of a poor prognosis is high, allocating the individual subject to subsequent antineoplastic treatment.

44. A method of detecting the uPA:PAI-1 complex in a sample, said sample selected from the group consisting of body fluids, normal cells, malignant cells, and tissues, said method comprising detecting the antigen comprising the uPA:PAI-1 complex by incubating the sample with one or more antibodies which specifically bind PAI-1 in the uPA:PAI-1 complex to form an antibody/antigen complex, and detecting

the antibody/antigen complex.

45. The method of claim 36 wherein PAI-1 protein abundance is determined in a sample of a body fluid.

46. A method according to claim 44 wherein the sample is a body fluid, and said body fluid is plasma.

47. A method according to claim 44 wherein the body fluid, normal or malignant cells, or other biological material is taken from a person suspected of having breast cancer.

48. A method according to claim 44 wherein the sample is a tissue.

49. A method of assaying the uPA:PAI-1 complex in a sample, said sample selected from the group consisting of body fluids, normal cells, malignant cells, and tissues, said method comprising assaying the antigen comprising the uPA:PAI-1 complex by incubating the sample with one or more antibodies which specifically bind PAI-1 in the uPA:PAI-1 complex to form an antibody/antigen complex, and assaying the antibody/antigen complex.

50. The method of 49, further comprising assaying the total amount of uPA in said sample.

51. A method of predicting the presence or progression of a malignant tumor in a subject having or suspected of having a malignant tumor, the method comprising

- (a) determining preoperatively PAI-1 protein abundance in a plasma sample from said subject
- (b) determining at least two weeks postoperatively PAI-1 protein abundance in a plasma sample from said subject,
- (c) determining the difference between the abundance of said PAI-1 protein determined preoperatively with the value determined at least two weeks postoperatively, and
- (d) correlating said difference with an established level of difference which is indicative of a high likelihood of tumor presence or metastasis.

52. A method according to claim 51 wherein the malignant tumor is a colon tumor.

53. A method of detecting the presence of a tumor in a subject suspected of having a tumor, the method comprising

- (a) determining at a first point in time (I) PAI-1 protein abundance in tumor tissue or a sample of a body fluid from said subject,
- (b) determining at a later point in time (II) PAI-1 protein abundance in a sample of body fluid from said subject,
- (c) determining the difference between the abundance of said PAI-1 protein determined at said first point in time (I) with the value determined at said later point in time (II), and
- (d) correlating said difference with an established level of difference which is indicative of a high likelihood of tumor presence.

54. A method according to claim 53, wherein the malignant tumor is selected from the group consisting of mammary carcinomas, urological carcinomas, gynaecological carcinomas, non-small cell lung tumors, gastrointestinal cancers, brain tumors, sarcomas, haematological malignancy and skin cancers.

55. The method of ~~claim 54~~ wherein PAI-1 protein abundance is determined in a sample of a body fluid.

56. The method of claim 2 where the marker is (ii).

57. The method of claim 3 where the marker is (ii).

58. The method of claim 4 where the marker is (ii).

59. The method of claim 5 where the marker is (ii).

60. The method of claim 2 where the marker is (iv).

61. The method of claim 3 where the marker is (iv).

62. The method of claim 4 where the marker is (iv).

63. The method of claim 5 where the marker is (iv).

64. The method of claim 7 where the marker is

determined using a sandwich ELISA.

65. The method of claim 64 in which, in said assay,



the PAI-1 is bound by an anti-PAI-1 monoclonal antibody.

66. The method of claim 65 in which said antibody is one which binds specifically to an antigenic determinant by human PAI-1 which is also specifically bound by a monoclonal antibody selected from the group consisting of those secreted by hybridoma clones 1-4.

67. The method of claim 66 in which the antibody is selected from the group consisting of the monoclonal antibodies secreted by hybridoma clones 1-4.

68. The method of claim 7 in which the complex is bound by an antibody which binds specifically to an antigenic determinant of human PAI-1 which is also specifically bound by the monoclonal antibody secreted by the hybridoma of clone 4 (ECACC 00112120).

69. The method of claim 68 in which the antibody is the monoclonal antibody secreted by the hybridoma of clone 4.

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